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Family History: A Comprehensive Genetic Risk Assessment Method for the Chronic Conditions of Adulthood

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Targeting individuals with increased risk for common, chronic disease can improve the efficiency and efficacy of preventive efforts by improving the predictability of screening tests and participant compliance. Individuals with the greatest risk for these disorders are those with a genetic susceptibility. The purpose of this study was to determine the feasibility of using a single, comprehensive family history as a method for stratifying risk for many preventable, common genetic disorders. Family histories obtained in a prenatal diagnostic clinic were reviewed regarding cardiovascular diseases, diabetes and several cancers; 42.5% of individuals reported a family history for at least one of the disorders under study. Familial coronary artery disease was most commonly reported (29% of participants), followed by noninsulin-dependent diabetes (14%). Qualitative characterization of disease susceptibility was also accomplished using family history data. For example, occurrence of different cancers within pedigrees was suggestive of familial cancer syndromes, and clustering of noninsulin-dependent diabetes and cardiovascular disease suggested an insulin resistance syndrome. Depending on the specific disease, 5 to 15% of at-risk individuals had a moderately increased risk (2 to 5 times the population risk), and approximately 1 to 10% had a high risk (absolute risks approaching 50%). Family history reports of common, chronic disease are prevalent among the population at large, and collection and interpretation of comprehensive family history data is a feasible, initial method for risk stratification for many preventable, chronic conditions. These findings may have important implications for disease prevention and management. Am. J. Med. Genet. 71:315–324, 1997.

KEY WORDS: prevention; screening; risk assessment; family history

INTRODUCTION

Cardiovascular diseases, diabetes and several cancers are among the leading causes of postnatal morbidity and mortality in developed countries such as the United States [American Heart Association, 1994; Wingo et al., 1995]. The loss of life and productivity caused by these disorders, as well as the tremendous financial burden incurred by their treatment, severely affects our economy and often devastates families. Health care administrators, policy makers, and providers are hopeful that preventive efforts against these common, chronic conditions will contain health care costs, and at the same time increase the quality of our public's health. Unfortunately, data supporting the efficacy and cost-effectiveness of current population-based screening guidelines for prevention of these disorders are controversial and incomplete. Areas of debate include: the appropriateness of mammography screening for women less than 50 years of age [Fletcher et al., 1993; Sickles and Kopans, 1995]; the utility of prostate-specific antigen screening [Whitmore, 1994]; the appropriateness of diabetes screening for early detection and prevention of associated complications [Singer et al., 1995; Knowler et al., 1995]; and the long-term benefits and risks of cholesterol screening and reduction [Goldman et al., 1992; Assmann and Schulte, 1990; Hulley et al., 1993; Smith et al., 1993].

Despite the controversies regarding population-based screening guidelines for chronic disease, it is clear that particular individuals with increased risk could benefit from preventive interventions. Generally, individuals with the greatest risk for developing many of these disorders are those with a genetic susceptibil-

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ity [King et al., 1992]. Thus, conventional preventive screening efforts in these individuals may be more efficient and efficacious [Morrison, 1992]. The efficiency of screening in genetically susceptible individuals may be increased due to improvement in predictive values of screening tests, as demonstrated in the case of breast cancer and colon cancer [Kerlikowske et al., 1993; Stephenson et al., 1993; Guillem et al., 1992; Houlston et al., 1990]. The efficacy of preventive efforts in these individuals may also improve because of increased participant compliance with recommended screening guidelines and therapies [Stephenson et al., 1993; Lynch et al., 1993; Bamberg et al., 1993]. In addition to benefitting from conventional prevention practices because of an increased magnitude in risk, genetically susceptible individuals may also benefit from enhanced screening protocols that involve more intensive screening methods, beginning at earlier ages, and occurring at more frequent intervals [Peters, 1991; NIH Consensus Development Panel on Ovarian Cancer, 1995; Vasen et al., 1993; Mecklin and Jarvinen, 1986]. This is because individuals with a genetic susceptibility for chronic disorders are more likely to have a severe disease phenotype characterized by an earlier age of onset, multifocal or bilateral disease, high rates of recurrence, and the occurrence of additional, related diagnoses [King et al., 1992].

Genetic susceptibility can be assessed by a variety of approaches, including DNA testing, biochemical and physiological testing, and personal and family history collection. Which method is most cost-effective for population-based, genetic risk assessment will be determined by the prevalence of a genetically determined disease, as well as by the accuracy, reliability and acceptability of the method for identifying high-risk, genetically susceptible individuals. Generally, physiological and biochemical genetic traits (e.g., colonic polyps and serum cholesterol) are not unique to genetically determined disease, and therefore are less powerful as initial markers for genetic risk assessment. Utilization of DNA markers for population-based, presymptomatic disease detection of chronic disorders does not yet appear to be feasible, and at this time, molecular testing is only indicated in the context of a family history of the disease [Hoskins et al., 1995; American Society of Human Genetics (ASHG) Ad Hoc Committee, 1994; National Advisory Council for Human Genome Research, 1994]. Thus, analysis of the family history appears to be the most appropriate method for the initial identification and stratification of genetic risk for common, chronic disorders.

As mentioned above, genetically susceptible individuals have an increased quantitative risk for many common, chronic conditions. In the case of heart disease, cancer and diabetes, the family history may reveal the magnitude of these disease risks. Typically, a family history of these disorders is associated with relative risks ranging from 2 to 5 times those of the general population [King et al., 1992]. Furthermore, for almost all of these conditions, an even greater increase in relative risk is associated with an increasing number of affected relatives, as well as with early ages of disease onset in relatives [King et al., 1992]. A small percentage of familial cases may be considered high risk, possibly representing dominantly inherited forms of disease. Clinically unaffected first-degree relatives in these families have absolute risks approaching 50%. When available, DNA mutation analysis within these families can have a profound influence in defining the magnitude of risk, and on recommendations for prevention.

Qualitative risk assessment or characterization of risk can also be accomplished by reviewing the family history. For instance, different phenotypic subsets of cardiovascular disease or cancer may be revealed by the family history. Aggregation of atherosclerotic cardiovascular disease, hypertension, dyslipidemia (increased triglycerides and decreased high density lipoprotein cholesterol), and impaired glucose tolerance or noninsulin-dependent diabetes is suggestive of an underlying familial trait of insulin resistance, often referred to as Syndrome X [Reaven, 1988]. Altered hemostasis may be suspected in a pedigree that features multiple affected relatives with early onset of coronary artery disease (CAD) and stroke or other thromboembolic events. The occurrence of different cancers within a family may be diagnostic of an inherited cancer syndrome such as the hereditary breast/ovary cancer syndrome, or hereditary nonpolyposis colorectal cancer (HNPCC), which is characterized by susceptibility to early-onset colon, gastric, endometrial, ureteral, ovarian, and biliary tract cancers [Watson and Lynch, 1993]. Consideration of these familial disease associations has important implications for identifying family members at risk and for recommending screening protocols for those individuals.

Accuracy of family history information has been investigated for coronary heart disease, diabetes and several cancers. In assessing the reliability of reported family histories of myocardial infarction, Kee et al. [1993] performed a case-control study in which reported histories of first-degree relatives were validated using death certificates, physician records, and hospital records. In the 174 cases, the sensitivity, positive predictive value, and specificity of a reported history of infarction in first-degree relatives were 67.3%, 70.5%, and 96.5%, respectively. These values did not differ significantly from the corresponding figures for the 175 controls (68.5%, 73.8%, and 97.7%, respectively). In this study, only small differences were observed between odds ratios based on reported and verified data, indicating that neither misclassification nor recall bias had a substantial impact on the measurement of the effect of the family history. The lower sensitivity values do indicate some under-reporting of disease in relatives; thus, a negative report should not be used as a definite indication of a minimum or decreased risk (below the general population risk). In a study assessing the accuracy of family history reports of diabetes, Hispanic and non-Hispanic white cases and controls were interviewed at clinic visits [Kahn et al., 1990]. Verification of these reports was obtained by subsequently interviewing family members. There was complete agreement between the information given by the proband regarding diabetic status and answers given by the respective family members. Love et al. [1985] have

studied the accuracy of patient reports of a family history of cancer. Verification of cancer histories was done by reviewing pathology and operative reports, hospital admission and discharge summaries, death certificates, and autopsy reports. Verification of negative histories was not performed. The accuracy of cancer site identification by the participant was 83.7% in first-degree, 71.3% in second-degree, and 71% in third-degree relatives. Participants were correct in 91% and 89% of the cases for all relatives in which they reported breast and colon as the primary sites, respectively. For first-degree relatives, 94% of reported breast cancer cases and 93% of colon cancer cases were confirmed. Overall, these studies suggest that a positive family history report can generally be used with a high degree of accuracy for the identification of individuals in the population who may be at increased risk for developing disease.

Because a family history is commonly reported for chronic conditions [King et al., 1992], and because it is an important qualitative and quantitative risk factor [King et al., 1992] that is generally accurately reported [Love et al., 1985; Acton et al., 1989; Kee et al., 1993], the systematic collection of family history information currently appears to be the most appropriate approach for identifying and stratifying genetic risk for many common, chronic diseases. To determine the feasibility of this approach as an initial step in the prevention of these disorders, a population-based, genetic risk assessment study was undertaken. Family histories of heart disease, stroke, hypertension, diabetes, breast cancer, colon cancer, ovarian cancer, endometrial cancer, and prostate cancer were obtained from a group of "healthy" young adults. The reporting frequencies of these disorders, and the proportion of high and moderate risk familial cases were evaluated, as was the ability to characterize disease susceptibilities in a qualitative fashion.

MATERIALS AND METHODS

Data Collection

Family history data were obtained from individuals attending the Prenatal Diagnostic Program at Cedars-Sinai Medical Center in Los Angeles. The prenatal/preconception counseling evaluation typically ascertains information regarding demographic data, and medical, obstetric and family histories from the participants (the consultands). A pedigree is drawn which includes information on first- and second-degree relatives of the consultands. Information regarding more distant relatives is obtained when appropriate, i.e., following a trait within the family or identifying relatives connecting the consultand and affected relative(s). The counseling focus is on problems that might affect the immediate health of the mother, fetus, or newborn infant.

For the purposes of this study, the genetic counselors received inservice training regarding the clinical presentations and genetic epidemiologic aspects of CAD, stroke, hypertension, noninsulin dependent diabetes (NIDDM), and on the familial cancers, including breast, ovarian, endometrial, colon, and prostate cancers. These disorders were chosen because of the strong role genetic susceptibility plays in their etiology, and because they are amenable to preventive measures [Lubin et al., 1990]. The counselors were then instructed to inquire about personal and family history information regarding these disorders, including age at disease onset, current age, or age at death.

The pedigrees of 200 couples who were seen sequentially after the inservice training were then reviewed. The reported prevalence rates of the selected diseases were assessed in all first- and second degree relatives in a four-generation pedigree, including the consultand's grandparents in generation I, the consultand's parents, aunts and uncles in generation II, the consultand, his/her siblings and half-siblings in generation III, and the consultand's offspring, nieces and nephews in generation IV.

Identifying and Stratifying Risk

Consultands reporting a family history of these disorders were considered to be at an increased risk (high risk or moderate risk) over the general population (Fig. 1). A positive family history was defined as having at least one affected first-degree relative, or two affected second-degree relatives in the same lineage. In addition, in the case of CAD, having a second-degree relative with premature disease (age of onset $\leq$55 years in males and $\leq$65 years in females) was also considered to place a consultand at high risk. An average risk (general population risk) was assigned to those individuals who reported only one affected paternal and/or maternal second-degree relative, or to those who did not report a family history of a selected disorder, including those who did not know their family history, or those who were adopted (one female consultand).

Once an at-risk family history was identified, the magnitude of disease susceptibility was derived from relative risk and empiric risk data [Fuchs et al., 1994; Claus et al., 1994; Colditz et al., 1993; Slattery and Kerber, 1993; Houlston et al., 1990, 1992a,b; Steinberg et al., 1990; Spitz et al., 1991; Carter et al., 1993; Nora et al., 1980; Rosenman et al., 1975; Slack and Evans, 1966; Rissanen, 1979; Graffagnino et al., 1994; Matias-Guiu et al., 1990; Spriggs et al., 1990; Pincus and White, 1993; Keen and Track, 1968; Working Party, College of General Practitioners, 1965], as well as by the recognition of characteristic single gene disorders within a pedigree. With this information, consultands were stratified into moderate and high risk groups, taking into consideration: (1) the degree of relationship of the affected relative(s); (2) the age at disease onset; (3) the sex of the consultand; and when appropriate, (4) the transmission of disease through either the maternal or paternal line. A pedigree was assigned a moderate risk level if the minimal criteria for an at-risk family history was satisfied (Fig. 1). The criteria to progress from a moderate to a high level of risk were specific for each disorder (see below).

For consultands reporting a family history of stroke, NIDDM, and colon cancer, a high risk was assigned to those with at least: (1) one first-degree relative with

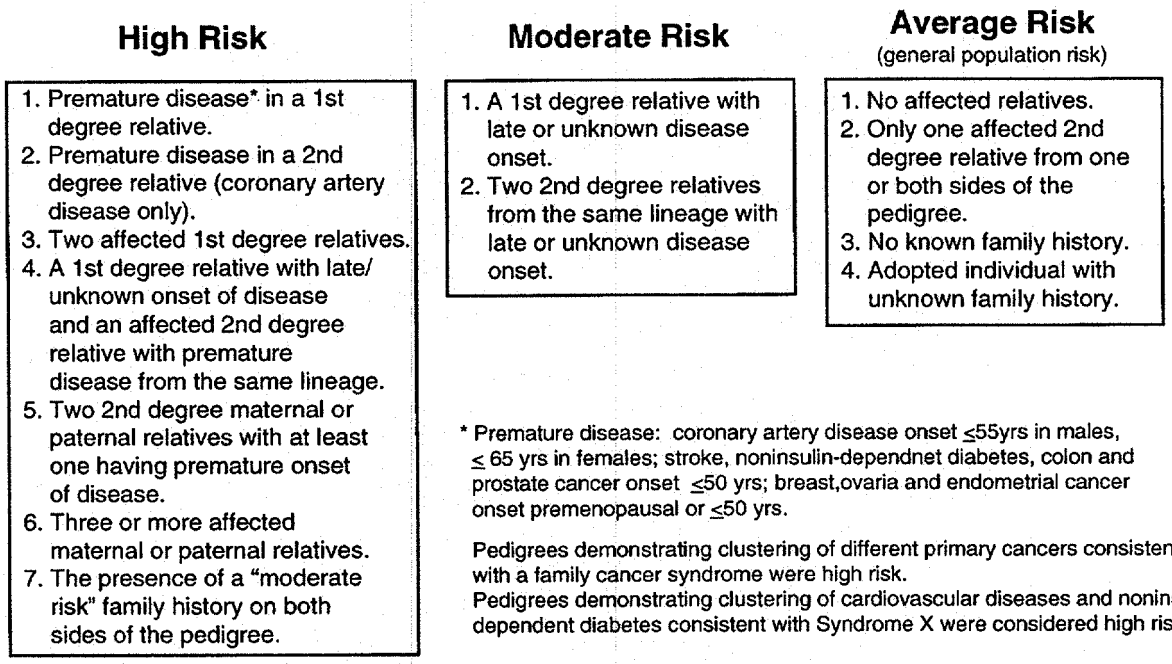

Fig. 1. General guidelines for risk stratification.

premature onset of disease; (2) two or more affected first-degree relatives; (3) a first-degree relative with late or unknown onset of disease and an affected second-degree relative with premature disease from the same side of the pedigree; (4) two second-degree maternal or paternal relatives with at least one having premature onset of disease; (5) three or more affected maternal or paternal relatives; or (6) a positive family history reported for both sides of the pedigree, i.e., any combination of an affected first-degree relative, two second-degree maternal or paternal relatives, or an affected second-degree relative with premature onset of disease. In the case of CAD, a high level of risk was also considered when a second-degree relative with premature disease alone was reported.

A subset of NIDDM, CAD and stroke family history reports were classified as an insulin resistance syndrome, Syndrome X [Reaven, 1988], when NIDDM was reported in combination with reports of CAD, stroke and/or hypertension in at least three family members in a common lineage. This was based on evidence from epidemiologic, family and twin studies that demonstrate excess aggregation of these traits within individuals and family members [Stout, 1990; Krolewski et al., 1981; Selby et al., 1991], each of which are associated with hyperinsulinemia [Reaven, 1988; Stout, 1990]. Because a family history of hypertension typically is underreported [Roseman et al., 1993], risk stratification for hypertension was not performed.

For the female-specific cancers (breast, endometrial, and ovarian), a high risk level was assigned if a consultand reported at least: (1) premenopausal disease onset (age less than 50) in a mother or sister; (2) premenopausal disease onset in a second-degree paternal relative; (3) premenopausal disease in a second-degree maternal relative and at least one other affected maternal relative; and (4) an affected mother or sister with postmenopausal onset and an affected maternal second-degree relative. With respect to prostate cancer, the only male-specific cancer, a similar scheme was followed. If the pedigree demonstrated clustering of different primary cancers consistent with a family cancer syndrome, they were also considered at high risk.

The overall ability to identify and stratify familial risk in asymptomatic individuals using these methods was assessed by contrasting the results to frequencies of family history reporting derived from the literature, i.e., disease-specific family histories reported in descriptive epidemiologic investigations and case-control studies. Whenever possible, comparisons were made with reported data collected from individuals of similar age. The literature frequencies were calculated by summing the number of cases reported divided by the number of subjects studied in each study.

Statistical Methods

Data analysis was performed using the SAS statistical software program [Statistical Analysis System (SAS), 1990]. Comparisons of disease frequencies between maternal and paternal relatives (including mothers and fathers) were assessed by chi-square contingency statistics [Dixon and Massey, 1983]. The proportion of positive family history reports for each study disorder, as well as the proportion of high risk pedigrees among those with a positive family history was compared with estimates from the literature and assessed by chi-square contingency statistics and the two-tailed Fisher's exact test [Fisher, 1934, 1970].

RESULTS

The characteristics of the consultands are summarized in Table I. The mean age for male and female consultands was 37.4 years (S.D. = 6.4 yr) and 34.9 years (S.D. = 4.4 yr), respectively. In general, the population was quite homogeneous; most were white (73%), married (93%), had professional or semiprofessional occupations (57%), and had insurance coverage for the visit (80%). Advanced maternal age was the most common reason for referral (56%), followed by parental concern for the pregnancy, an abnormal screening result for maternal serum alpha-fetoprotein (MSAFP), and family history of a genetic disease (none of which were the selected disorders evaluated in this study). Seventeen percent of the male consultands were absent from the counseling session, and their medical and family history information was provided by their partner. Only 3% of consultands reported having one of the disorders under evaluation.

Information was collected on 5,812 first- and second-degree relatives; 2,787 were relatives of the male consultands and 3,025 were relatives of the female consultands. The average pedigree size was 14.5 individuals. As detailed in Table II, most diagnoses of interest (CAD, stroke, hypertension, NIDDM, and cancers) were reported in the older generations. This is not surprising since the prevalence of these disorders increases with age. The most commonly reported disease in these older generations (generations I and II) was CAD, with a prevalence of 9.0%, followed by hypertension (4.1%), NIDDM (3.7%), colon cancer (0.9%), breast cancer (4.2% of female relatives), and prostate cancer (2.2% of male relatives).

Table III summarizes the disease prevalence for first- and second-degree relatives in generations I and II, contrasting the maternal and paternal sides of the pedigrees. Based on higher disease rates reported in parents compared to other relatives, it appears that the consultands in general know more about their first-degree than their second-degree relatives. Hypertension, which is usually an asymptomatic disease, appears much more likely to be reported among the parents than the second-degree relatives, whereas disorders with more apparent clinical sequelae (cancers and stroke) are more evenly reported. For each of the diseases, there were no statistically significant differences between the reported disease rates in maternal versus paternal second-degree relatives (grandparents, aunts and uncles). However, in first-degree relatives (mothers and fathers), there were significant reporting differences for CAD, with 19.3% (74/384) of fathers versus 5.1% (20/394) of mothers reported as affected; $P < 0.001$. This difference in reporting a CAD history in parents is not surprising, since women gen-

TABLE I. Characteristics of the Consultands

Number of consultands present for counseling	
Female	200
Male	166
Age	
Female	34.9 yrs (S.D. = 4.4, range = 18–44)
Male	37.4 yrs (S.D. = 6.4, range = 22–66)
Ethnicity (%)	
Caucasian	73
African American	6
Asian	9
Hispanic	8
Unknown	4
Marital status (%)	
Married	93
Reason for referral[a] (%)	
Advanced maternal age	56
Concern	13
Abnormal MSAFP[b]	11
Family history of genetic disease	9
Other	11
Occupation (%)	
Professional/semiprofessional	57
Homemaker	9
Other	14
Unknown	20
Billing (%)	
Insured (private or HMO)[c]	80
State program funding	10
Other	8
Unknown	2
Health status (%)	
Personal common disease history	3

[a]None referred because of a family history of common disease.
[b]MSAFP, maternal serum alpha-fetoprotein.
[c]HMO, health maintenance organization.

TABLE II. Prevalence of Chronic Conditions by Generation (%)

Disease	I (n = 401)	II (n = 2,361)	III (n = 1,551)	IV (n = 1,499)	Total relatives (n = 5,812)
CAD[a]	18	8	0.3	—	5
Stroke	4	1	0.1	—	0.8
Hypertension	3	4	0.8	0.1	2
NIDDM[b]	5	4	0.3	—	2
Colon cancer	2	0.7	—	—	0.4
Breast cancer[c]	5	4	—	—	4
Endometrial cancer[c]	0.5	0.4	0.1	—	0.6
Ovarian cancer[c]	2	0.3	0.5	—	0.4
Prostate cancer[c]	5	2	—	—	1

[a]CAD, coronary artery disease.
[b]NIDDM, noninsulin-dependent diabetes.
[c]Sex-specific cancers limited to female/male relatives; one male relative had breast cancer.

erally develop CAD approximately 10 years later than men. The sex-specific cancers had obvious reporting differences, with prostate cancer reported in fathers, and breast, ovarian, and endometrial cancers reported in mothers (with the exception of one case of breast cancer occurring in a father).

One-hundred seventy of the 400 reported family histories placed the respective consultands at higher risk than the general population (Table IV); 32.5% (130/400) of the consultands were identified to be at increased risk for one common genetic disease, an additional 8.2% (33/400) were found to be at risk for two disorders, and 1.8% (7/400) were at risk for three disorders. The risk for CAD occurred most frequently (29% of all consultands) followed by NIDDM (14% of all consultands). Most consultands with positive family histories were at moderate risk (i.e., relative risk of approximately 2 to 5), as compared to the general population (Table V). However, depending upon the disease, approximately 1% to 10% of individuals were at high risk (absolute risks approaching 50%).

Twenty-nine percent (116/400) of the consultands were identified to be at an increased risk for CAD. Stroke was reported in 5.2% (6/116) of these pedigrees, and Syndrome X was reported in 17.2% (20/116). There were an additional 13 pedigrees reporting a family history of isolated stroke and five additional Syndrome X pedigrees that did not report a family history of CAD (for a total of 25 Syndrome X pedigrees).

Of the 19 (4.8%) consultands reporting a family history of stroke, 21% were at high risk, and 79% were at moderate risk. Approximately one-third of consultands reporting a family history of stroke also had a family history of CAD.

A family history of NIDDM was reported by 14% (56/400) of the consultands; 30% (17/56) were considered to be at high risk, and 70% (39/56) were at moderate risk. A family history consistent with Syndrome X was reported in 45% (25/56) of the these pedigrees.

Seven consultands (1.8%), reported a family history of colon cancer. An autosomal dominant pattern of transmission was inferred in one of the pedigrees; therefore, it was considered to be high risk. The remaining six pedigrees were assigned a moderate risk.

Fourteen women had significant family histories of breast cancer; half of them (3.5% of all female consultands) were considered to have a high level of risk. One pedigree was consistent with the familial breast/ovary cancer syndrome, an autosomal dominant disorder. This was the only pedigree in which a family history of ovarian cancer was reported. The remaining half of the familial breast cancer cases were considered

TABLE III. Disease Prevalence in Maternal and Paternal Relatives (%)†

	Parent		Aunt/uncle/grandparent	
Disease	Father (n = 384)	Mother (n = 394)	Paternal (n = 1,016)	Maternal (n = 916)
CAD[a]	19.3*	5.1*	8.2	8.6
Stroke	2.1	1.3	1.7	1.3
Hypertension	9.1	13.2	1.5	1.1
NIDDM[b]	6.5	5.3	3.2	2.4
Colon cancer	0.8	0.8	0.8	1.2
Breast cancer	0.3	5.6	1.9	1.0
Endometrial cancer	n/a[c]	1.8	0.5	—
Ovarian cancer	n/a	0.3	0.3	0.1
Prostate cancer	1.8	n/a	0.8	1.1

†Other than one father with breast cancer, the sex-specific cancers (breast, endometrial, ovarian, prostate) were reported in females or males as expected.
*The prevalence of CAD is greater in fathers than mothers; $P < 0.001$.
[a]CAD, coronary artery disease.
[b]NIDDM, noninsulin-dependent diabetes.
[c]n/a, not applicable.

TABLE IV. Family Histories of Common Chronic Disease

Disease	No. of positive[a] family histories	Percent of pedigrees with positive[a] family histories (total = 170)	Percent of total pedigrees (n = 400)
CAD[f]			
Isolated CAD	90	52.9	22.5
With stroke	6	3.5	1.5
With Syndrome X	20	11.8	5.0
Subtotal	116	68.2	29.0
Stroke			
Isolated stroke	13	7.7	3.3
With CAD	6	3.5	1.5
Subtotal	19	11.2	4.8
NIDDM[g]			
Isolated NIDDM	31	18.2	7.8
With Syndrome X	25	14.7	6.2
Subtotal	56	32.9	14.0
Colon cancer	7	4.1	1.8
Breast cancer	14	8.2/15.6[b]	7.0[c]
Endometrial cancer	7	4.1/7.8[b]	3.5[c]
Ovarian cancer	1	0.6/1.1[b]	0.5[c]
Prostate cancer	1	0.6/1.3[d]	0.5[e]

[a]For definition of a positive family history, see Methods. Does not include a male consultand's significant family history of breast cancer in a father.
[b]Proportion of females with a positive family history, n = 90.
[c]Female consultands only, n = 200.
[d]Proportion of males with a positive family history, n = 80.
[e]Male consultands only, n = 200.
[f]CAD, coronary artery disease.
[g]NIDDM, noninsulin-dependent diabetes.

to be at moderate risk. One male consultand had a history of a father with breast cancer.

Seven (3.5%) female consultands reported a family history of endometrial cancer; one was considered to be high risk, and six were at moderate risk. A family history of prostate cancer was reported by only one male consultand, and in this family it appeared to be transmitted as an autosomal dominant trait.

Five additional pedigrees were identified as potentially at risk for known Mendelian genetic disorders. One pedigree had multiple relatives affected with peptic ulcer disease segregating in a dominant fashion, suggestive of a dominant form of this disease, such as the Zollinger-Ellison syndrome. In another pedigree, relatives were reported to have an "ear tumor," a "chest tumor," and skin lesions, suggestive of neurofibromatosis. One consultand reported that he and a sib had "juvenile polyps," and that several maternal relatives had histories of gastrointestinal malignancies, raising the likely diagnosis of dominantly inherited juvenile polyposis. A report of multiple paternal relatives with "arthritis of the back" was suggestive of ankylosing spondylitis, and a pedigree suggestive of familial pancreatic cancer was also described.

TABLE V. Proportion (%) of Consultands at Average, Moderate, and High Risk

Disease	Risk		
	Average	Moderate	High
CAD[a]	71.0	17.8	11.2
Stroke	95.2	3.8	1.0
NIDDM[b]	86.0	9.8	4.2
Colon cancer	98.3	1.5	0.2
Breast cancer[c]	93.0	3.5	3.5
Endometrial cancer[c]	96.5	3.0	0.5
Ovarian cancer[c]	99.5	—	0.5
Prostate cancer[d]	99.5	—	0.5

[a]CAD, coronary artery disease.
[b]NIDDM, noninsulin-dependent diabetes.
[c]In 200 female consultands.
[d]In 200 male consultands.

Prevalence of Familial Disease: Assessing Study Methods

The reporting of family histories and the proportion of high-risk cases were compared to the frequencies of familial disease and high-risk familial disease reported in epidemiologic studies of specific disorders (see Table VI). In general, the reporting frequencies in the current study were similar to previously reported estimates. However, in the present study, stroke, NIDDM, and prostate cancer were reported significantly less frequently than in the literature. This is likely due to the younger age of the study population; the consultands' relatives may not have been old enough to develop these late-onset disorders. Additionally, in the case of prostate cancer, the frequency reported by Spitz et al. [1991] in the relatives of control subjects may have been overestimated because the controls themselves had other forms of cancer which may, in some cases, have been linked with prostate cancer [Spitz et al., 1991]. Frequencies of familial endometrial cancer and ovarian cancer in asymptomatic individuals were not available from the literature.

Among those individuals who reported a family history for a given disease, the proportion of high risk families was also examined. When compared to estimates from disease-specific epidemiologic studies, the proportions of high-risk familial diseases in the present study were often quite similar. Unfortunately, data regarding high-risk familial disease estimates were not available for comparison for either NIDDM or stroke. Because of the infrequent reporting of familial ovarian cancer and prostate cancer in the present study, it was not possible to accurately compare the prevalence of high risk familial disease.

DISCUSSION

This study has demonstrated that review of the family history reports from 400 "healthy" consultands ascertained via a prenatal diagnostic clinic is a feasible method of identifying and stratifying genetic risk for many common, preventable disorders of adulthood; 42.5% (170/400) of the consultands had a family history of at least one of the selected common disorders (130 individuals were at risk for one disorder, 33 were at risk for two disorders, and 7 were at risk for three disorders), and an additional five family histories were suggestive of other autosomal dominant conditions. The estimates of familial disease prevalences were substantial and generally similar to expected values derived from the literature, confirming the accuracy of this comprehensive screening tool. Although most con-

TABLE VI. Prevalence of Familial Disease and Proportion of High Risk Familial Cases†

	Familial disease		High risk familial cases†	
	Present study	Literature estimates[a]	Present study	Literature estimates[b]
CAD[f]	29% (116/400)	25% (19/75)	39% (45/116)	38% (86/228)[c]
Stroke	5% (19/400)**	22% (126/583)**	21% (4/19)	N/A
NIDDM[g]	14% (56/400)*	20% (101/514)*	30% (30/56)	N/A
Colon cancer	2% (7/400)	3% (68/1,976)	14% (1/7)	17% (32/192)
Breast cancer	7% (14/200)	5% (219/4,083)	50% (7/14)	52% (259/502)
Endometrial cancer	3.5% (7/200)	N/A[e]	14% (1/7)	47% (7/15)
Ovarian cancer	<1% (1/200)	N/A	100% (1/1)	19% (123/639)
Prostate cancer	<1% (1/200)	7% (73/1,023)[d]	100% (1/1)	33% (34/104)

†Proportion of familial cases that are high risk among all familial cases.
*$P < 0.05$; **$P < 0.01$.
[a]Estimates are derived from family history data of the control groups in relative risk studies; references: Duncan and Kyle [1982]; Lynch et al. [1973]; Stephenson et al. [1991]; La Vecchia et al. [1992]; Slattery and Kerber [1993]; Steinberg et al. [1990]; Spitz et al. [1991]; Graffagnino et al. [1994]; Matias-Guiu et al. [1990]; Spriggs et al. [1990]; Keen and Track [1968]; Rose [1964].
[b]Estimates derived from family history data of familial cases described in the literature; references: Slattery and Kerber [1993]; Houlston et al. [1992a]; Steinberg et al. [1990]; Nora et al. [1980]; Houlston et al. [1992b]; Ponz de Leon et al. [1992]; Mecklin [1987]; Greggi et al. [1990]; Sandles et al. [1992]; Boltenberg et al. [1990]; Genest et al. [1992]; Grover et al. [1973].
[c]Proportion of familial lipid disorders in cases with premature heart disease (CAD onset prior to age 56 [Nora et al., 1980] and prior to age 60 [Genest et al., 1992]).
[d]Individuals with other cancers.
[e]N/A, not available.
[f]CAD, coronary artery disease.
[g]NIDDM, noninsulin-dependent diabetes.

sultands had an average (general population) risk for any given disorder, approximately 5% to 15% of consultands were at moderate risk, and 1% to 10% were at high risk. The ability to recognize the higher risk familial cases is validated by the similarities in estimates when comparing the current data with estimates from the literature. This study also demonstrated the ability to recognize important familial disease associations, thereby allowing for a qualitative characterization of disease risk. It should be emphasized that the power of this method is enhanced when at least a four-generation pedigree is obtained, including information regarding all first- and second-degree relatives.

Not surprisingly, cardiovascular disease was the most frequently occurring risk to the study population. Cardiovascular disorders (CAD, stroke, and Syndrome X) accounted for 79% (134/170) of the positive family histories. Family history not only identified individuals at risk but also allowed for the recognition of phenotypic subsets of cardiovascular disease, such as Syndrome X which accounted for almost one-fifth of the cardiovascular family history reports, and a possible thromboembolic subgroup featuring the aggregation of stroke and CAD which was reported in 14% of these family histories.

Individuals from these phenotypic subgroups of cardiovascular disease may be characterized further by biochemical analyses, allowing for further risk stratification. For example, in asymptomatic relatives from pedigrees that are suggestive of insulin resistance (Syndrome X), screening for evidence of abnormal carbohydrate metabolism and the associated characteristic dyslipidemia (decreased HDL, increased triglycerides, and increased small, dense low density lipoprotein [LDL]) may be useful in identifying at-risk family members [Austin et al., 1988; Reaven et al., 1993]. In families with CAD and stroke or other thromboembolic events, abnormalities involving hemostasis should be considered in addition to lipid abnormalities. A wide range of heritable hemostatic defects may be implicated, including altered levels and activity of protein C, protein S, antithrombin III, fibrinogen, plasminogen, tissue plasminogen activator, plasminogen activator inhibitor-1, resistance to activated protein C, and elevated homocyst(e)ine levels [Jensen and Ens, 1990; Svensson and Dahlback, 1994; Berg et al., 1992].

Familial cancers accounted for 18% (30/170) of the consultands' positive family histories, several of which were suggestive of dominant cancer conditions. Even in pedigrees in which only one type of cancer has occurred, the consultand may be at an increased risk for other cancers in addition to the cancer reported in the family history. For example, a woman who has a paternal history of early-onset colon cancer may be at an increased risk for breast cancer as well as colon cancer [King, 1990], and male consultands with a family history of breast cancer have a 1.5-fold increased risk for prostate cancer [Tulinius et al., 1992]. Awareness of these risks and associations may encourage the individual to pursue at minimum the level of screening recommended for the general public, and it may justify the use of earlier and more intensive screening efforts in these individuals. In pedigrees suggestive of a hereditary condition featuring cancer risks, such as HNPCC, site-specific breast cancer or breast/ovary cancer, enhanced screening for the associated cancer diagnoses would be indicated, beginning at earlier ages, with increased frequency, and with more intensive surveillance techniques than those recommended for the general population [Vasen et al., 1993; NIH Consensus Development Panel on Ovarian Cancer, 1995; King et al., 1993]. Furthermore, individuals from cancer pedigrees may be candidates for DNA mutation analysis (e.g., BRCA1, BRCA2, MSH2, MLH1) which may further refine their cancer risks.

Obtaining a comprehensive family history that includes information regarding the common, chronic disorders of adulthood should be an integral component of

any disease prevention program. This is a comprehensive, acceptable, and generally accurate approach for risk stratification for many preventable, common disorders that can impact a large proportion of the population. Individuals identified in this manner will have the most to gain from preventive interventions and are likely to benefit from earlier, more intensive screening. Furthermore, since individuals from these families often overestimate their risks [Garber et al., 1993], they are likely to be reassured by accurate genetic risk information.

Clearly, genetics professionals who routinely obtain extensive family histories in their daily practice should incorporate information regarding common, chronic conditions within their patients' pedigrees. As this study indicates, a significant proportion of their patients will likely have family histories warranting a preventive medicine referral, and/or consideration of DNA mutation analysis.

Unfortunately, primary care physicians, who will play an increasingly important role in genetic risk assessment for common disorders, most often obtain family history information in order to support an already suspected diagnosis rather than as a means to predict disease risk [Roseman et al., 1993]. Failure to recognize the importance of the family history for disease risk prediction and prevention may result from a general lack of genetics knowledge [Hoffman et al., 1993] as well as from underappreciation of the role genetics plays in the development of chronic conditions of adulthood. Because of the significant impact genetic susceptibility information may have on disease management and prevention, it is vitally important that the public, health care professionals and administrators become educated regarding the importance of the family history as a tool for assessing genetic susceptibilities for chronic diseases.

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